

# Medical Management of Parkinson's Disease

Marvin M. Goldenberg, PhD, RPh, MS

## INTRODUCTION

Parkinsonism is a clinical syndrome characterized by at least two of four cardinal features: bradykinesia (slowness and minimal movement), rigidity, resting tremor (trembling), and an impairment of postural balance leading to disturbance of gait and falling.<sup>1</sup> The most common type of parkinsonism is idiopathic Parkinson's disease (PD), first described by James Parkinson, an English physician, in 1817 as paralysis agitans (the shaking palsy). Dr. Parkinson described the major symptoms of the disease that would later bear his name. For the next century and a half, scientists pursued the causes and treatment of the disease, defining its range of symptoms, its distribution among the population, and its prospects for cure.

The pathological hallmark of PD is a loss of the pigmented, dopaminergic neurons of the substantia nigra pars compacta in the brain, with the appearance of intracellular inclusions known as Lewy bodies.<sup>2,3</sup> In the early 1960s, researchers identified a fundamental defect that is a hallmark of the disease: the loss of brain cells that produce an important chemical, dopamine, which helps direct muscle activity. Progressive loss of dopamine-containing neurons is a feature of normal aging; however, most people do not lose the 70% to 80% of the dopaminergic neurons required to cause symptomatic PD.<sup>4</sup> Without treatment, PD progresses over 5 to 10 years to a rigid, akinetic state in which patients are incapable of caring for themselves. Death may result from complications of immobility, such as aspiration pneumonia and pulmonary embolism.

Pharmacological attempts to restore dopaminergic activity with levodopa and dopamine agonists have been successful in alleviating many of the clinical features of PD. An alternative but complementary approach has been to restore the normal balance of cholinergic and dopaminergic influences on the basal ganglia with anticholinergic drugs. The availability of effective pharmacological treatment has radically altered the prognosis of PD; in most cases, good functional mobility can be maintained for many years, and the life expectancy of adequately treated patients is increased substantially.

## EPIDEMIOLOGY

PD is a progressive disorder of the central nervous system (CNS), and it affects 1 to 1.5 million people in the U.S.<sup>5,6</sup> The annual incidence of idiopathic PD increases from about 20 per 100,000 persons in the fifth decade of life to about 90 per 100,000 persons in the seventh decade of life. The approximate age of onset is 60 years.<sup>7</sup> Extensive epidemiological research



Marvin M.  
Goldenberg,  
PhD, RPh, MS

of idiopathic PD suggests that environmental factors such as rural living, drinking well water, and heavy metal and hydrocarbon exposure have small but demonstrable contributions to the risk of idiopathic PD. Interestingly, cigarette smoking, caffeine consumption, and nonsteroidal anti-inflammatory drug use are associated with protection against the illness.<sup>8</sup>

The cumulative exposures to supposed toxins, factors associated with aging of the CNS, or other yet uncharacterized cell death mechanisms may be responsible for the onset of PD in later life and for its progression. Genetic factors may play a role, particularly if the disease begins before age 50. Nine genetic linkages and four genes have so far been identified in PD.<sup>9</sup>

Society pays an enormous price for PD. According to the National Parkinson Foundation, each patient spends an average of \$2,500 a year for medications.<sup>5</sup> After factoring in office visits, Social Security payments, nursing-home expenditures, and lost income, the total cost to the nation is estimated to exceed \$6 billion annually.<sup>10</sup>

PD affects approximately 50,000 Americans each year and more than 500,000 at any one time. Obtaining an accurate count of the number of cases may be impossible, however, because many people with early-stage disease assume that their symptoms are the result of normal aging and they do not seek help from a physician. Diagnosis is also difficult because symptoms of other conditions resemble those of PD. Doctors may initially tell patients that they have another disorder; conversely, patients with a similar disease may be initially told that they have PD.

PD strikes men somewhat more often than women.<sup>7</sup> PD knows no social, economic, or geographic boundaries. Some studies show that PD is less common in African-Americans and Asians than in Caucasians.<sup>11</sup> Scientists have not been able to explain this apparent lower incidence in certain populations, but it is reasonable to assume that all people face a similar risk.

## ETIOLOGY

Parkinson's disease occurs when certain nerve cells in the substantia nigra (i.e., "black substance") region of the brain die or become impaired and degenerate.<sup>12</sup> Normally, these neurons produce dopamine, a chemical messenger responsible for transmitting signals between the substantia nigra in the basal ganglia and the next "relay station" of the brain, the corpus striatum, to generate smooth, purposeful muscle activity. Loss of dopamine causes the nerve cells of the striatum to fire out of control, leaving patients unable to direct or control their movements in a normal manner. In patients with PD, 60% to 80% or more of dopamine-producing cells in the substantia nigra may be lost. The cause of this cell death or impairment is not clear.<sup>13</sup>

Although the pathogenesis of PD is unknown, one mecha-

*The author is President of Pharmaceutical and Scientific Services at Marvin M. Goldenberg, LLC, in Westfield, New Jersey. His e-mail address is marvinmgoldenberg@verizon.net.*

Accepted for publication May 14, 2008.

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nism of toxicity to the substantia nigra that may play a role is the creation of cellular damage from oxyradicals.<sup>14</sup> Dopamine generates free radicals from auto-oxidation and from monoamine oxidase (MAO) metabolism. Normally, several anti-oxidative mechanisms are present within and outside the neurons to limit any damage that might be evoked by an attack by free radicals, but such protection may be overwhelmed or impaired in PD. Excitotoxicity, programmed activation of cell death, and chronic infection are also under consideration as the etiologic mechanism of PD.<sup>15</sup>

Some scientists have suggested that PD occurs when either an external or an internal toxin selectively destroys dopaminergic neurons.<sup>16</sup> An environmental risk factor, such as exposure to pesticides or a toxin in the food supply, is an example of an external trigger that might cause PD. The theory is based on the fact that a number of toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and neuroleptic drugs, induce parkinsonian symptoms in humans. So far, however, no research has provided conclusive proof that a toxin is the cause of the disease.

The cause of nerve cell degeneration in PD has not been identified. Genetics may play a small role. Studies of toxic models of PD and the genes implicated in inherited forms of PD point to two major pathogenetic mechanisms: (1) misfolding and aggregation of proteins and (2) mitochondrial dysfunction leading to oxidative stress.<sup>16</sup>

*LRRK2* is the first gene that is frequently mutated in autosomal-dominant late-onset PD.<sup>17</sup> Genetic causes have been identified with several distinct mutations. Recently, nine mutations involving a novel gene, leucine-rich repeat kinase 2 (*LRRK2*), have been identified as the cause of autosomal-dominant PD in kindreds, and some of them have been previously linked to the *PARK8* locus on chromosome 12. *LRRK2* mutations are relatively common genetic causes of familial and sporadic PD.

These mutations have also been identified in diverse populations. The clinical and pathological features of *LRRK2*-associated PD are indistinguishable from those of idiopathic PD; however, considerable clinical and pathological variability exists even among kindreds.<sup>18</sup>

Mutations in the gene encoding *LRRK2* have been recently linked with autosomal-dominant parkinsonism, which is clinically indistinguishable from typical, idiopathic, late-onset PD. Thus, the protein *LRRK2* has emerged as a promising therapeutic target for treatment. *LRRK2* is large and complex, with multiple enzymatic and protein-interaction domains, each of which is targeted by pathogenic mutations in familial PD.<sup>19</sup>

Several genes identified in familial PD ( $\alpha$ -synuclein, parkin, and ubiquitin carboxy-terminal hydroxylase L1) encode for proteins involved in the ubiquitin-proteasome system, which is responsible for normal degradation and clearance of proteins in eukaryotic cells. Mutations in these genes appear to be linked to mishandling and accumulation of proteins, which in turn leads to cell death.<sup>16</sup>

The potential role of mitochondrial dysfunction and subsequent oxidative stress in the pathogenesis of PD was first suggested by the discovery that the administration of MPTP, a mitochondrial electron transport chain inhibitor, to rodents

and primates, produced a phenotype similar to that observed in PD. Inhibition produces toxic products, including harmful reactive oxygen species that can cause cellular damage by reacting with proteins, lipids, and nucleic acids.<sup>16</sup>

A relatively new theory explores the role of genetic factors in the development of PD. From 15% to 20% of PD patients have a close relative who has experienced parkinsonian symptoms, such as a tremor.<sup>20,21</sup> Several causative genes have been identified, usually eliciting young-onset parkinsonism. However, identified genetic and familial forms of PD are rare. Mutations in the gene for the protein  $\alpha$ -synuclein, located on chromosome 4, result in autosomal-dominant parkinsonism. The function of this protein is not known. The most commonly occurring genetic defect affects the gene for the protein called parkin on chromosome 6.<sup>22</sup> Mutations in this gene result in autosomal-recessive parkinsonism, which is slowly progressive with onset before the age of 40.

Mutations in the parkin gene are the most common cause of familial parkinsonism, and a growing number of studies are showing that stress factors associated with sporadic PD promote parkin accumulation in the insoluble fraction. Parkin and  $\alpha$ -synuclein accumulation and mutations in these genes have been associated with familial PD. Accumulation of  $\alpha$ -synuclein might contribute to the pathogenesis of PD and other Lewy body diseases by promoting alterations in parkin and tubulin solubility, which in turn might compromise neural function by damaging the neuronal cytoskeleton. Such findings provide a new perspective on the potential nature of pathogenic  $\alpha$ -synuclein and parkin interactions in PD.<sup>22</sup>

### DIAGNOSIS

There are no practical diagnostic laboratory tests for PD; the diagnosis rests on the clinical features or by excluding other causes of parkinsonism.

Fluorodopa positron emission tomography (PET) measures levodopa uptake into dopamine nerve terminals, showing a decline of about 5% per year of striatal uptake. This diagnostic test reveals decreased dopaminergic nerve terminals in the striatum in both PD and the Parkinson-plus syndromes but does not distinguish between them. A marked response to levodopa is helpful in the differential diagnosis, indicating presynaptic dopamine deficiency with intact postsynaptic dopamine receptors, features typical of PD.<sup>23</sup>

Computed tomography (CT) and magnetic resonance imaging (MRI) may be performed to determine a structural disorder as the cause of symptoms. The diagnosis of PD is likely if drug treatment results in improvement.<sup>16</sup>

The diagnosis of PD is based on clinical symptoms. Mild, early disease may be difficult to recognize because it usually begins subtly. Detecting PD is especially difficult in older people because aging can cause similar problems, such as loss of balance, slow movements, muscle stiffness, and stooped posture.

PD develops insidiously and progresses slowly in most patients. Symptoms such as tremor at rest can be intermittent in the beginning, becoming present only in stressful situations.<sup>23</sup> Patients with PD can live 20 or more years, depending on the age at onset; the mortality rate is about 1.5 times that

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of normal individuals the same age. Death from PD usually results from a concurrent unrelated illness or from the effects of decreased mobility, aspiration, or increased falling with subsequent physical injury.

### SYMPTOMS

PD is a motor system disorder. The four primary symptoms are tremor (trembling) in the hands, arms, legs, jaw, and face; rigidity or stiffness of the limbs and trunk; bradykinesia (slowness of movement); and postural instability (impaired balance and coordination).<sup>20,24</sup> As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing simple tasks. Other symptoms include an expressionless face, reduced manual dexterity, handwriting difficulties, drooling, sleep problems, urination at night, depression and anxiety, constipation, and difficulty turning in bed at night.

The disease is chronic and progressive, but it does not affect everyone in the same way. PD may appear to be progressing faster in some patients than in others. Some patients become severely disabled; others experience only minor disruptions in motor functions.

### Motor (Physical) Symptoms

**Tremor.** Tremor is the primary symptom for some patients, but it might be only a minor complaint for others, for whom other symptoms may be more troublesome. The tremor associated with PD typically takes the form of a rhythmic back-and-forth motion of the thumb and forefinger at three beats per second. This is sometimes called “pill rolling.” Tremor usually begins in a hand, although sometimes a foot or the jaw is affected first. It is most obvious when the hand is at rest or when the patient is under stress. In 75% of patients, the tremor may affect only one part or side of the body, especially early in the disease; in later stages, tremor may become more generalized. Tremor is rarely disabling, and it usually disappears during sleep or improves with intentional movement.

**Rigidity.** Resistance to movement affects most PD patients. A major principle of body movement is that all muscles have an opposing muscle. Movement is possible not just because one muscle becomes more active, but because the opposing muscle relaxes. Rigidity comes about when, in response to signals from the brain, the delicate balance of opposing muscles is disturbed. The muscles remain constantly tensed and contracted so that the person aches or feels stiff or weak. Rigidity is the increased muscular resistance to passive range of motion, and it often has a “cogwheel” quality.<sup>20</sup> When a limb is moved by the examiner, it resists, then gives way in small, step-like movements as if it were being controlled by a cogwheel.<sup>25</sup>

**Bradykinesia.** The loss of spontaneous and automatic movement is particularly frustrating because it is unpredictable; one moment the patient can move easily but the next moment he or she may need help. This may well be the most disabling and distressing symptom of the disease because the patient cannot perform routine movements quickly. Activities that could previously be performed easily—such as washing or dressing—may take several hours.

**Postural instability.** Impairment in balance and coordination causes patients to lean forward or backward and to fall easily. When bumped from the front or when starting to walk, patients

who lean backward tend to step backward (retropulsion). A stooped posture may develop in which the patient's head is bowed and the shoulders are drooped. As the disease progresses, walking may be affected. Patients may halt in mid-stride and “freeze” in place, possibly even toppling over, or they may walk with a series of quick, small steps as if hurrying forward to keep balance (festination).

### Non-Motor Symptoms

Many symptoms can be treated with appropriate medication or physical therapy. No one can predict which symptoms will affect an individual patient, and the intensity of the symptoms also varies among patients. None of these symptoms is fatal, but they affect quality of life.<sup>13,20</sup>

**Depression.** Depression may appear early in the course of the disease, even before other symptoms are noticed. It might not be severe, but it may be intensified by the drugs used to treat other symptoms of PD. Fortunately, depression can be successfully treated with antidepressant medications. Depression is also discussed under Cognitive Changes later.

**Emotional changes.** Some people with PD become fearful and insecure. They may not want to travel or socialize. Some lose their motivation and become apathetic and dependent on family members. Others may become irritable or uncharacteristically pessimistic. Memory loss and slow thinking may occur, although the ability to reason remains intact. Whether people actually suffer intellectual loss or dementia from PD is a controversial area still being studied.

**Dysphagia.** Muscles used in swallowing may work less efficiently in later stages of the disease. Food and saliva may collect in the mouth and at the back of the throat, which can result in choking or drooling. Medications such as levodopa and apomorphine can often alleviate these problems.

**Dysarthria.** About 50% of all PD patients have problems with speech. They may speak too softly or in a monotone, hesitate before speaking, slur or repeat their words, or speak too fast. A speech therapist may be able to relieve some of these problems.

**Urinary problems or constipation.** In some patients, bladder and bowel problems can result from improper functioning of the autonomic nervous system, which regulates smooth-muscle activity, and from adverse drug effects. Some patients may become incontinent, whereas others have trouble urinating. Constipation may occur because the gastrointestinal (GI) tract operates more slowly; it can also be caused by inactivity, eating a poor diet, or drinking too little fluid. It can be persistent, and, in rare cases, can be serious enough to require hospitalization. Patients should not let constipation last for more than a few days before taking steps to alleviate it.

**Skin problems.** It is common for the patient's skin to become oily, particularly on the forehead and at the sides of the nose. The scalp may become oily too, resulting in dandruff. In other cases, the skin can become very dry. These problems result from an improperly functioning autonomic nervous system. Standard dermatological treatments can help. Excessive sweating, also common, is usually controllable with medications used for PD.

**Fragmented sleep.** Sleep problems include difficulty staying asleep at night, restless sleep, nightmares, and drowsiness

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during the day. It is unclear whether these symptoms are related to PD or to the medications used to treat PD. Patients should never take over-the-counter sleep aids without consulting a physician.

### Cognitive Changes

PD is a complex condition accompanied by numerous symptoms. Primary symptoms involve changes in movement, but other symptoms can occur as well. Changes in one's ability to think, reason, and remember may develop, and many factors can contribute to these differences.<sup>26</sup>

Cognitive changes can affect patients' everyday lives as much as, and sometimes more than, the physical (motor) effects of PD.<sup>27</sup> Even though physicians are increasingly recognizing the importance of addressing cognitive and other non-motor symptoms, many still primarily focus on treating physical symptoms and cognitive changes may remain undertreated or untreated. An accurate assessment of cognitive changes is needed in order to establish an appropriate treatment strategy.

**Thinking.** Bradyphrenia, or a slowing of the ability to think, can occur.<sup>26</sup> Just as it takes more time to rise from a chair, patients may need more time to respond intellectually. It takes longer to process information, and this can lead to frustration for both patients and caregivers. Bradyphrenia may be misinterpreted as intentional behavior, a lack of interest, or even stubbornness, but it is important to understand that changes in the brain are the cause of the symptom.

Pressuring an individual who is having problems of cognition creates stress and usually makes matters worse. Patients may find it difficult to think of other ways of doing things or to shift from one topic to another. These changes in cognition may be mistaken as intentional, and the individual may be labeled as being rigid or inflexible. In some patients, a portion of the brain involved in this type of thinking can be affected.

**Memory.** Memory remains relatively unaffected in PD, although some individuals may have trouble remembering where and when particular events occurred if they are not given a cue. For example, patients recall information much better if they are given multiple choices to select from, and they benefit from using cues more than people of a similar age without PD.

**Language.** Significant language changes are uncommon in PD, but subtle changes may occur. Speech often becomes slower, and spontaneous speech is reduced. Patients might not initiate conversations as often, if at all. These changes can be misinterpreted as indifference and can result in poor communication.

**Dementia.** Significant and dramatic changes in memory, reasoning ability, language, and attention may develop in a small number of patients.<sup>27,28</sup> As people age, the risk of a progressive decline in the ability to think and remember increases. If dementia develops, patients need increased care and supervision.

**Depression.** Depression is another possible cause of cognitive changes in patients with PD, and it is more common in these patients than in the general population; 25% of PD patients experience depression within one year of the onset of PD symptoms.<sup>26</sup> The development of depressive symptoms is unlikely to be a result of difficulty adjusting to the diagnosis

alone. Several symptoms of PD are similar to the symptoms of depression (e.g., loss of interest in activities, fatigue, change in weight, and social withdrawal). This similarity can result in an underdiagnosis of depression in those with PD. Furthermore, patients might not even recognize that they are depressed. On a more positive note, depression is treatable and can be controlled with a combination of antidepressant medications and cognitive-behavioral therapies. If left untreated, depression can have serious negative consequences, interfering with cognition and, consequently, with quality of life.

### Adverse Drug Reactions

As will be discussed later, many types of medications are available to control PD symptoms. However, managing the symptoms of PD becomes increasingly difficult as the illness progresses. The development of adverse effects and changes in the steady response to medications pose numerous challenges to patients, their families, and health care providers. Unfortunately, changes in cognitive ability can be a potential side effect of all drugs used to treat PD. Therefore, patients must know which side effects are associated with the drugs they are taking. If cognitive decline is experienced, a health care provider should be notified immediately.

### Summary

Some patients with PD experience changes in mood and cognitive ability. The most common changes include slowed thinking and processing of information. A decreased ability to generate new ways of solving problems may be apparent. While changes in memory are less frequent, some people with PD forget where and when the information was obtained but remember the information itself. Dementia develops in some patients, and advancing age is a risk factor. Depression is often underdiagnosed in these patients. Regardless of the type of cognitive changes experienced, accurate assessment is essential if symptoms are to be treated.

### PATIENT ASSESSMENT

Early symptoms of PD are subtle and occur gradually.<sup>1</sup> Patients may be tired, or they may experience a general malaise. Some may feel a little shaky or have difficulty getting out of a chair. They may notice that they speak too softly or that their handwriting looks cramped and spidery. They may lose track of a word or thought, or they may feel irritable or depressed for no apparent reason. This early period may last a long time before the more classic and obvious symptoms appear.

Friends or family members may be the first to notice changes. They may see that the person's face lacks expression and animation ("masked face") or that the person remains in a certain position for a long time or does not move an arm or leg normally. Perhaps they see that the person seems stiff, unsteady, and unusually slow.

The onset of symptoms may go unnoticed for several years. Early signs include stiffness of fingers or a stiff shoulder accompanied by stiff muscles. Pain may be a feature.<sup>20,23</sup> Symptoms usually only affect one side of the body for one to two years and then spread to the other side. Tremor is often noticed first and usually provokes the initial visit to the doctor. How-



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ever, up to 30% of patients do not have tremor; this can lead to a misdiagnosis. As the disease progresses, the tremor that affects most patients may begin to interfere with daily activities.<sup>1</sup>

Patients may not be able to hold utensils steady or may find that the shaking makes reading a newspaper difficult. The tremor may become worse when the patient is relaxed. Shaking is most pronounced a few seconds after the hands are rested on a table.

### MEDICAL TREATMENT

Medications are the most common therapy for PD.<sup>12,20,23</sup> The goal is to correct the shortage of dopamine; it is this deficiency that causes the symptoms. Pharmacological treatment is usually started when symptoms become disabling or disrupt daily activities. Treatments may differ according to the patient's symptoms, age, and responses to specific drugs. It often takes time to find the best combination of drugs for each patient.

#### Levodopa and Levodopa/Carbidopa

Levodopa (L-dopa, L-3,4-dihydroxyphenylalanine), the metabolic precursor of dopamine, is the single most effective agent for treating PD. Levodopa itself is largely inert; both its therapeutic and adverse effects result from decarboxylation of levodopa to dopamine.

When taken orally, levodopa is absorbed rapidly from the small bowel by the transport system for aromatic amino acids. Drug concentrations in the plasma usually peak between 0.5 and 2 hours after an oral dose. The half-life in plasma is short (one to three hours). The rate and extent of absorption of levodopa depend on the rate of gastric emptying, the pH of gastric juice, and the length of time the drug is exposed to the degradative enzymes of the gastric and intestinal mucosa. Competition for absorption sites in the small bowel from dietary amino acids may also affect the absorption of levodopa; taking levodopa with meals delays absorption and reduces peak plasma concentrations.

Entry of the drug into the CNS across the blood-brain barrier is also mediated by a membrane transporter for aromatic amino acids, and competition between dietary protein and levodopa may occur at this level. In the brain, levodopa is converted to dopamine by decarboxylation primarily within the presynaptic terminals of dopaminergic neurons in the striatum. The dopamine produced is responsible for the therapeutic effectiveness of the drug in PD; after release, it is either transported back into dopaminergic terminals by the presynaptic uptake mechanism or is metabolized by the actions of monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

In clinical practice, levodopa is almost always given in combination with a peripherally acting inhibitor of aromatic L-amino acid decarboxylase, such as carbidopa or benserazide (not available in the U.S.), which does not penetrate well into the CNS. If levodopa is administered alone, the drug is largely decarboxylated by enzymes in the intestinal mucosa and other peripheral sites, so that relatively little unchanged drug reaches the cerebral circulation and probably less than 1% penetrates the CNS.

Dopamine release into the circulation by peripheral conver-

sion of levodopa also elicits undesirable effects, particularly nausea. Circulating plasma concentrations of dopamine stimulate the brainstem's chemoreceptive trigger zone to induce nausea. This effect is usually reversible with drugs that inhibit peripheral dopa-decarboxylase.

Inhibition of peripheral decarboxylase elevates the fraction of administered levodopa that remains unmetabolized and available to cross the blood-brain barrier and reduces the incidence of GI adverse effects. In most individuals, a daily dose of carbidopa 75 mg is sufficient to prevent nausea. For this reason, the most commonly prescribed form of carbidopa plus levodopa (e.g., Sinemet, Bristol-Myers Squibb; Atamet, Elan) is carbidopa 25 mg/levodopa 100 mg. With this formulation, dosage schedules of three or more tablets daily provide acceptable inhibition of decarboxylase in most individuals. Occasionally, patients require larger doses of carbidopa to minimize GI adverse effects, and supplemental carbidopa (Lodosyn, Merck) alone may be beneficial.

**Effectiveness.** Levodopa therapy can have a dramatic effect on all the signs and symptoms of PD. Early in the course of the disease, the degree of improvement in tremor, rigidity, and bradykinesia may be nearly complete. In early PD, the duration of the beneficial effects of levodopa may exceed the plasma lifetime of the drug, suggesting that the nigrostriatal dopamine system retains some capacity to store and release dopamine. A principal limitation of long-term levodopa therapy is that this apparent buffering capacity is lost over time and the patient's motor state may fluctuate dramatically with each dose of levodopa.

A common problem is the development of the "wearing-off" phenomenon; each dose of levodopa effectively improves mobility for a period of time, perhaps one to two hours, but rigidity and akinesia quickly return at the end of the dosing interval. Increasing the dose and frequency of administration can improve the situation, but this approach is often limited by the development of dyskinesia (excessive and abnormal involuntary movements). Dyskinesia is usually observed when plasma levodopa levels are high, although dyskinesia or dystonia can also be triggered when levodopa levels are rising or falling. These movements can be as disabling as the rigidity and akinesia of PD. In later stages of PD, patients may fluctuate rapidly between being "off," or experiencing no beneficial effects from medication, and being "on," but with disabling dyskinesias (the "on/off" phenomenon).

It is still unknown whether levodopa alters the course of the underlying disease or merely modifies symptoms. Two aspects of treatment and outcomes are of concern.

First, if the production of free radicals, as the result of dopamine metabolism, contributes to the death of nigrostriatal neurons, the addition of levodopa can accelerate the process, although no convincing evidence for this effect has yet been obtained.

Second, the undesirable on/off and wearing-off phenomena are observed almost exclusively in patients receiving levodopa, but it is not known whether delaying treatment with levodopa delays the appearance of these effects. Because of these uncertainties, most physicians have adopted a pragmatic approach and use levodopa only when PD symptoms cause functional impairment.

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**Adverse effects.** In addition to motor fluctuations and nausea, a common and troubling adverse event with levodopa treatment is the induction of hallucinations and confusion, which are common in the elderly and in those with pre-existing cognitive dysfunction.<sup>29</sup> The presence of these effects often limits the ability to treat parkinsonism symptoms adequately. Recently, atypical antipsychotic agents have been used in such patients, such as quetiapine (Seroquel, AstraZeneca) and clozapine (Clozaril, Novartis), although other agents can worsen PD.<sup>29</sup>

Peripheral decarboxylation of levodopa and the release of dopamine into the circulation may activate vascular dopamine receptors and produce orthostatic hypotension.<sup>29</sup> The actions of dopamine at alpha-adrenergic or beta-adrenergic receptors may induce cardiac arrhythmias, especially in patients with pre-existing conduction disturbance. Taking levodopa with nonspecific inhibitors of MAO, such as phenelzine (Nardil, Pfizer) and tranylcypromine (Parnate, GlaxoSmithKline), accentuates the actions of levodopa and may precipitate a life-threatening hypertensive crisis and hyperpyrexia.

Levodopa is currently considered the most effective drug for controlling symptoms of PD, and for many years, it was the preferred drug for treating newly diagnosed PD. However, because its long-term use at high dosages may lead to motor complications that can be difficult to manage, many physicians switch to dopamine-receptor agonists (see next column). Approximately 40% of patients who are receiving levodopa develop motor fluctuations after four to six years of treatment.<sup>30</sup>

Table 1 shows the various levodopa drug combinations and initial dosing available in the U.S.

### Carbidopa/Levodopa/Entacapone (Stalevo)

Stalevo (Novartis) is a combination tablet for patients who experience end-of-dose wearing-off. Even though carbidopa reduces the side effects of levodopa, entacapone (Comtan, Novartis) extends the time levodopa is active in the brain (up to 10% longer).<sup>31,32</sup> Entacapone prolongs the availability of levodopa in the plasma, and thus to the brain, by decreasing

its peripheral *O*-methylation and by slowing its elimination rate, without affecting the maximum plasma levodopa concentration or the time to maximum concentration.<sup>32</sup> The same drugs that interact with carbidopa/levodopa and entacapone interact with Stalevo.

### Dopamine-Receptor Agonists (Bromocriptine, Ropinirole, Pramipexole, Apomorphine)

Drugs acting directly on dopamine receptors may also have a beneficial effect.<sup>16</sup> Unlike levodopa, dopamine-receptor agonists do not require enzymatic conversion to an active metabolite, have no potentially toxic metabolites, do not compete with other substances for active transport into the blood and across the blood-brain barrier, and do not depend on the functional capacities of the nigrostriatal neurons.<sup>16</sup> In addition, drugs selectively affecting certain (but not all) dopamine receptors may have more limited adverse effects than levodopa.

Finally, if the hypothesis that free radical formation as a result of dopamine metabolism contributes to neuronal death is correct, dopamine-receptor agonists may be able to modify the course of the disease by reducing the endogenous release of dopamine as well as the need for exogenous levodopa.

### Oral Agents

Three oral dopamine-receptor agonists are available for the treatment of PD: an older agent, bromocriptine (Parlodel, Novartis), and two newer, more selective compounds, ropinirole (Requip, GlaxoSmithKline) and pramipexole (Mirapex, Pfizer). Another agent, pergolide (Permax, Valeant; Par, Teva), was removed from the market in 2007.

**Bromocriptine.** As an ergot derivative, bromocriptine is a strong agonist of the D<sub>2</sub> class of dopamine receptors, and it is a partial antagonist of the D<sub>1</sub> receptors. It is available as a 2.5-mg tablet and a 5-mg capsule. It has been used with carbidopa/levodopa (Sinemet) to reduce symptoms and ameliorate the adverse reactions associated with long-term levodopa therapy. Bromocriptine is still available, but it is not as effective as other dopamine agonists early in PD, and it is not useful in late-stage PD for reducing motor fluctuations caused by levodopa.

**Ropinirole and pramipexole.** These two agents have selective activity at D<sub>2</sub> class sites (specifically at the D<sub>2</sub> and D<sub>3</sub> receptor proteins) and little or no activity at D<sub>1</sub> class sites. These drugs, like bromocriptine, are well absorbed orally and have similar therapeutic actions. Like levodopa, they can relieve the clinical symptoms of PD. The duration of action of the dopamine agonists (8 to 24 hours) is often longer than that of levodopa (6 to 8 hours), and these agents are particularly effective in treating on/off phenomena. All three drugs may also produce hallucinosis or confusion, similar to that observed with levodopa, and they may worsen orthostatic hypotension.<sup>12</sup>

The therapeutic effects of these agents are related to actions at postsynaptic dopamine receptors, but they can also activate presynaptic autoreceptors found on dopamine terminals, which are mainly of the D<sub>2</sub> class. By stimulating presynaptic receptors, pramipexole and ropinirole may lower endogenous dopamine produc-

**Table 1 Levodopa Drug Combinations for the Treatment of Parkinson's Disease**

Medication	Available Doses	Initial Dosing
Carbidopa/levodopa (Sinemet)	10/100 mg 25/100 mg 50/250 mg	25/100 mg two to three times per day
Carbidopa/levodopa controlled-release (Sinemet CR)	50/250 mg	50/250 mg twice daily
Carbidopa/levodopa/entacapone (Stalevo)	12.5/50/250 mg 25/100/250 mg 37.5/150/250 mg 50/200/200 mg	12.5/50/250 mg
Carbidopa/levodopa orally disintegrating tablet (Parcopa)	10/100 mg 25/100 mg 25/250 mg	25/100 mg two or three times per day

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tion and release, thereby diminishing oxidative stress.

It takes several weeks to achieve clinically significant maintenance doses of ropinirole and pramipexole.<sup>12</sup> These agents generally evoke less disturbance of the GI tract than bromocriptine, but they can elicit nausea and somnolence. The somnolence may be severe, and sudden attacks of irresistible sleepiness leading to motor vehicle accidents have been reported.<sup>33</sup>

The introduction of pramipexole and ropinirole has led to a substantial change in the clinical use of dopamine agonists in PD. Because these selective agonists are well tolerated, they are used increasingly as an initial treatment for PD rather than as adjuncts to levodopa. This change has been driven by two factors: (1) dopamine agonists have a longer duration of action and may be less likely than levodopa to evoke on/off effects and dyskinesias, and (2) levodopa may contribute to oxidative stress, thereby accelerating the loss of dopaminergic neurons.

In two large controlled clinical trials comparing levodopa with pramipexole or ropinirole as an initial therapy for PD, a reduced rate of motor fluctuation in patients receiving these agonists was evident.<sup>34,35</sup> However, this benefit was accompanied by an increased rate of adverse events in both studies, especially somnolence and hallucinations.<sup>34,35</sup>

Many specialists now favor dopamine agonists as an initial treatment as monotherapy in patients with early PD and in younger patients to reduce motor fluctuations and dyskinesia. Levodopa should be used as the initial treatment in older patients, who might be more vulnerable to the adverse cognitive effects of the dopamine agonists.

**Adverse effects (ropinirole).** In early PD trials, the most commonly observed adverse events associated with ropinirole affecting more than 5% of patients were, in order of decreasing incidence, as follows: nausea, dizziness, somnolence, headache, vomiting, syncope, fatigue, dyspepsia, viral infection, constipation, pain, increased sweating, asthenia, dependent or leg edema, orthostatic symptoms, abdominal pain, pharyngitis, confusion, hallucinations, urinary tract infections, and abnormal vision.<sup>36</sup>

In advanced PD trials, the most commonly observed adverse events associated with ropinirole as an adjunct to levodopa in more than 5% of patients were, in order of decreasing incidence, as follows: dyskinesias, nausea, dizziness, aggravated parkinsonism, somnolence, headache, insomnia, injury, hallucinations, falls, abdominal pain, upper respiratory infection, confusion, increased sweating, vomiting, viral infection, an elevated drug level, arthralgia, tremor, anxiety, urinary tract infection, constipation, dry mouth, pain, hypokinesia, and paresthesia.<sup>36</sup>

**Adverse effects (pramipexole):** In placebo-controlled trials of early PD, the most commonly observed adverse events that were more numerous with pramipexole in more than 5% of patients were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations, dizziness, somnolence, extrapyramidal syndrome, headache and confusion), and gastrointestinal symptoms (e.g., nausea).<sup>37</sup>

In placebo-controlled trials of advanced PD, the most com-

monly observed adverse events that were more frequent with pramipexole and concomitant levodopa in more than 5% of patients were postural hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency.<sup>37</sup>

### An Injectable Medication

**Apomorphine (Apokyn).** Motor fluctuations are distressing for patients with advanced PD. Subcutaneous apomorphine injections can be a valuable adjunctive therapy.<sup>38</sup> Apomorphine HCl (Mylan/Bertek) is a fast-acting dopaminergic agonist after it is injected subcutaneously. It has high affinity for D<sub>4</sub> receptors; moderate affinity for D<sub>2</sub>, D<sub>3</sub>, D<sub>5</sub>, and adrenergic  $\alpha$ 1D,  $\alpha$ 2B, and  $\alpha$ 2C receptors; and low affinity for D<sub>1</sub> receptors. It is approved as a rescue therapy for the acute intermittent treatment of "off" episodes in patients with a fluctuating response to dopaminergic therapy.

Apomorphine can be injected when muscles become frozen and the patient cannot rise from a chair or perform daily activities. Treatment with as-needed injections may make it possible to decrease the doses of other anti-PD medications. This may reduce the risk of side effects, such as twitching and other uncontrolled movements. Apomorphine can be taken with an antinausea drug to prevent side effects of severe nausea and vomiting.

Apomorphine is available only from selected pharmacy distribution centers, and an office or clinic-based test dose with monitoring for blood pressure (BP) and tolerability is required. Table 2 lists some dopamine agonists and the initial dosing schedule.

**Adverse effects.** In addition to all the other potential adverse effects associated with dopamine receptor agonists, apomorphine is highly emetogenic and can cause QT prolongation, injection-site reactions, hallucinations, dyskinesia, and abnormal behavior.<sup>16</sup> It is recommended that trimethobenzamide (Tigan, King), an oral antinauseant and antiemetic agent, be started at a dose of 300 mg three times daily three days before the initial apomorphine dose and continued at least during the first two months of therapy. The use of apomorphine with antiemetic drugs of the serotonin (5-HT<sub>3</sub>) antagonist class is contraindicated because of reports of profound hypotension and loss of consciousness when ondansetron (Zofran, Glaxo-SmithKline) and apomorphine are taken together.<sup>39</sup>

### A Transdermal Patch

**Rotigotine Transdermal System (Neupro).** The Neupro patch (UCB/Schwarz) was approved in 2007 to treat the signs and symptoms of early-stage idiopathic PD.<sup>40</sup> Neupro is the first once-daily, non-ergolinic, dopamine agonist patch to provide stable, continuous drug delivery 24 hours per day.<sup>16</sup> Therapeutic benefits are independent of age, sex, and race.

Available in three strengths (2 mg every 24 hours, 4 mg every 24 hours, and 6 mg every 24 hours), the patch is designed to mimic the action of dopamine. Multinational clinical studies in patients with early-stage PD were completed at the end of 2003. In 15 clinical trials, more than 1,500 patients used the patch. Rotigotine exhibits a low potential of pharmaco-

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**Table 2 Dopamine Agonists for the Treatment of Parkinson's Disease**

Medication	Available Doses	Initial Dosing	Target Maintenance Dose
Apomorphine HCl (Apokyn injection)	0.02–0.06 mL	0.02 mL during “off” periods	3–6 mg three times per day
Rotigotine transdermal system (Neupro)	2 mg every 24 hours 4 mg every 24 hours 6 mg every 24 hours	One 2-mg patch per day	4–6 mg every 24 hours
Pramipexole (Mirapex)	0.125 mg 0.25 mg 0.5 mg 1 mg 1.5 mg	0.125 mg three times per day	1.5–4.5 mg/day
Ropinirole (Requip)	0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg 5 mg	0.25 mg twice daily	5 mg twice daily

kinetic drug–drug interactions.

**Adverse effects.** Frequently reported adverse events in clinical trials were nausea, application-site reactions, somnolence, dizziness, headache, vomiting, and insomnia. Other adverse effects included peripheral edema, fluid retention, hallucinations, symptomatic orthostatic hypotension, weight gain, elevated heart rate, elevated BP, and syncope.<sup>40</sup>

Despite the agent's benefits, the manufacturer informed health providers and patients that by the end of April 2008, the patch would not be available from pharmacies in the U.S. The recall was based on reports of the possibility of reduced clinical performance because of rotigotine crystals forming in the patches, resulting in less drug absorption through the skin and in the potential for lower efficacy.

### Catechol-O-Methyltransferase Inhibitors (Tolcapone and Entacapone)

COMT-inhibitors are a relatively new class of drugs for treating PD.<sup>24</sup> COMT and MAO are responsible for the catabolism of levodopa as well as dopamine. COMT transfers a methyl group from the donor S-adenosyl-L-methionine, producing the pharmacologically inactive compounds 3-O-methyl-dopa (from levodopa) and 3-O-methoxytyramine (from dopamine). When levodopa is administered orally, nearly 99%

of the drug is catabolized and does not reach the brain. Most is converted by aromatic L-amino acid decarboxylase (AAD) to dopamine, which causes nausea and hypotension.

The addition of an AAD-inhibitor such as carbidopa reduces the formation of dopamine but increases the amount of levodopa, which is methylated by COMT. The principal therapeutic action of the COMT-inhibitors is to block this peripheral conversion to levodopa to 3-O-methyl-dopa, elevating both the plasma half-life of levodopa as well as the fraction of each dose that reaches the CNS.

Two COMT-inhibitors are presently marketed in the U.S.: tolcapone (Tasmar, Valeant) and entacapone (Comtan). Both agents reduce the clinical symptoms of “wearing off” in patients taking levodopa/carbidopa.<sup>41,42</sup> Although the magnitude of their clinical effects and their mechanisms of action are the same, their pharmacokinetic properties and adverse events differ. Tolcapone has a relatively long duration of action (two or three times a day) and acts by both central and peripheral inhibition of COMT. It significantly reduces “off” time an average of 40% and

increases total “on” time by about 25% at all dose levels. Levodopa/carbidopa dosage and frequency can be decreased.

Entacapone's duration of action is short (approximately two hours), and it is usually taken simultaneously with each dose of levodopa/carbidopa. The drug's action is attributable mainly to its peripheral inhibition of COMT.

Table 3 shows the initial dosing schedule for these two COMT inhibitors.

**Adverse effects.** The effects of tolcapone and entacapone are similar to those observed with levodopa/carbidopa alone and include nausea, orthostatic hypotension, vivid dreams, confusion, and hallucinations.<sup>43,44</sup> Both agents have been known to cause increases in serum alanine aminotransferase and aspartate transaminase (ALT and AST). A notable adverse effect is diarrhea. Hepatotoxicity may occur with tolcapone, and a warning label is included in the prescribing information. Tolcapone should be used with extreme caution. Because of the risk of potentially fatal, acute fulminant liver failure, tolcapone should usually be used in patients taking levodopa/carbidopa who are experiencing symptom fluctuations and who are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies. Entacapone has not been associated with hepatotoxicity.

In placebo-controlled trials associated with tolcapone, the most commonly observed adverse events in more than 5% of patients but not seen at an equivalent frequency among placebo-treated patients were dyskinesia, nausea, sleep disorders, dystonia, excessive dreaming, anorexia, muscle cramps, orthostatic complaints, somnolence, diarrhea, confusion, dizziness, headache, hallucination, vomiting, constipation, fatigue, upper respiratory tract infection, falling, increased sweating, urinary tract infections, xerostomia, abdominal pain, and urine discoloration.<sup>43</sup>

**Table 3 Catechol-O-Methyltransferase (COMT)–Inhibitors for the Treatment of Parkinson's Disease**

Medication	Available Doses	Initial Dosing
Entacapone (Comtan)	200 mg	200 mg with levodopa; maximum 8 per day
Tolcapone (Tasmar)	100 mg 200 mg	100 mg three times per day



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In placebo-controlled trials associated with entacapone, the most commonly observed adverse events affecting more than 5% of patients were dyskinesia and hyperkinesia, nausea, urine discoloration, diarrhea, and abdominal pain.<sup>44</sup>

### Selective Monoamine Oxidase-B Inhibitors (Selegiline and Rasagiline)

Two isoenzymes of MAO oxidize monoamines. Although both isoenzymes (MAO-A and MAO-B) are present in the periphery and inactive monoamines of intestinal origin, the isoenzyme MAO-B is the predominant form in the striatum and is responsible for most of the oxidative metabolism of dopamine in the brain.

**Selegiline.** At low-to-moderate doses (10 mg/day or less), selegiline (Eldepryl, Watson) is a selective inhibitor of MAO-B, resulting in irreversible inhibition of the enzyme.<sup>45</sup> Unlike nonspecific inhibitors of MAO (such as phenelzine, tranylcypromine and isocarboxazid), selegiline does not inhibit peripheral metabolism of catecholamines; therefore, it can be administered safely with levodopa. Selegiline also does not cause the lethal potentiation of catecholamine action when patients taking nonspecific MAO inhibitors ingest directly acting sympathomimetic amines, such as the tyramine found in aged or fermented cheeses and some red wines. Doses higher than 10 mg daily can elicit inhibition of MAO-A and should be avoided.

Selegiline has been used for several years as a symptomatic treatment for PD, although its benefit is modest. The basis of the efficacy of selegiline is presumed to be its capacity to slow the metabolism of dopamine in the striatum.

Selegiline is generally well tolerated in patients with early or mild PD. In patients with more advanced PD or underlying cognitive impairment, selegiline may accentuate the adverse motor and cognitive effects of levodopa therapy. Metabolites of selegiline include amphetamine and methamphetamine, which may cause anxiety, insomnia, and other adverse symptoms.

**Adverse effects.** Experience with selegiline obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to receive selegiline, compared with 50 patients assigned to receive placebo, in the only parallel-group, placebo-controlled trial of patients with PD were nausea, dizziness, lightheadedness, and fainting; abdominal pain; confusion; hallucinations; dry mouth; vivid dreams; dyskinesias; and headache.<sup>45</sup>

**Zydis selegiline.** Zelapar (Valeant), an orally disintegrating tablet, includes a patented delivery system.<sup>46</sup> Zydis technology allows the tablet to dissolve within seconds in the mouth upon contact with saliva. The active drug undergoes pregastric absorption through the oral mucosa and thus largely bypasses the intestine, obviating the need for first-pass hepatic metabolism. It can be taken once daily, up to 2.5 mg/day. Fewer amphetamine-like metabolites and possibly fewer adverse events are produced with a lower dose, typically 1.25 mg.<sup>47</sup>

**Rasagiline.** A related compound, rasagiline (Agilect, Azilect, Teva) is an oxidase type-B (MAO-B) inhibitor that also blocks the breakdown of dopamine,<sup>48</sup> but it does not form undesirable metabolites. Rasagiline tablets are indicated for treating signs

and symptoms of PD, both as initial therapy alone and as an addition to levodopa later in the disease. The 1-mg formulation is available in 30 countries, including the U.S., Canada, Israel, Mexico, and most European countries.

Rasagiline was approved for use as an initial single drug therapy in early PD, and as an addition to levodopa in patients with more advanced disease. Initially, rasagiline was said to be associated with hypertensive crisis if patients also consume tyramine-rich foods (e.g., aged cheeses, fermented bean curd) and beverages (e.g., some red wines, beer, ale) or dietary supplements or amines contained in many cough and cold medications.

It was assumed that all nonselective MAO inhibitors were associated with dietary tyramine interactions that would result in hypertensive reactions. To test the safety of rasagiline, challenges with tyramine 50 to 75 mg were performed in 72 rasagiline-treated and 38 placebo-treated PD patients at the end of two double-blind, placebo-controlled trials (TEMPO and PRESTO; see page 604). An abnormal pressor response was prespecified as three consecutive measurements of systolic BP increases of 30 mm Hg or more and bradycardia of 40 beats/minute or less.

In one substudy involving 55 patients with early PD receiving rasagiline monotherapy, no patients assigned to rasagiline (1 mg/2 mg; n = 38) or placebo (n = 17) developed systolic BP or heart rate changes indicative of a tyramine reaction.<sup>49</sup> In the second substudy involving 55 levodopa-treated patients, 3 of 22 subjects receiving rasagiline 0.5 mg/day and one of 21 subjects receiving placebo developed asymptomatic, self-limiting systolic BP elevations of 30 mm Hg or greater on three measurements. None of the 12 patients receiving rasagiline 1 mg/day experienced significant BP or heart rate changes after ingesting tyramine. These data demonstrate that rasagiline 0.5 to 2 mg daily was not associated with clinically significant tyramine reactions and that it could be used as monotherapy or as an adjunct to levodopa in patients without specific dietary tyramine restrictions.<sup>49</sup>

As with most other medications for PD, rasagiline has the potential to cause involuntary movements (dyskinesias), hallucinations, and lowered BP.

**The ADAGIO Study.** The Attenuation of Disease Progression with Agilect/Azilect Once Daily (ADAGIO) study, the first of its kind, was prospectively designed to demonstrate whether rasagiline could slow the progression of PD.<sup>50</sup> Early treatment with once-daily rasagiline 1-mg tablets provided significant clinical benefits not obtained by those patients when the initiation of rasagiline therapy was delayed by nine months.

ADAGIO, a randomized, multicenter, double-blind, placebo-controlled, parallel-group study, was prospectively conducted to examine rasagiline's potential disease-modifying effects in 1,176 patients with early, untreated PD. Patients from 129 centers in 14 countries were randomly assigned to early treatment (72 weeks of rasagiline therapy 1 or 2 mg once daily) or delayed treatment (36 weeks of placebo, followed by 36 weeks of rasagiline 1 or 2 mg once daily, in the active-treatment phase).

The primary analyses of the trial were based on a change in total scores on the Unified Parkinson's Disease Rating Scale (UPDRS) and included slope superiority of rasagiline over placebo in the placebo-controlled phase, change from baseline

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**Table 4 Monoamine Oxidase-B (MAO-B)–Inhibitors for the Treatment of Parkinson's Disease**

Medication	Available Doses	Initial Dosing
Selegiline (Eldepryl, Carbox)	5 mg	5 mg twice daily (maximum dose)
Selegiline HCl orally disintegrating tablets (Zelapar)	1.25 mg 2.5 mg	1.25 mg once daily
Rasagiline (Agilect)	0.5 mg 1 mg	0.5 mg once daily

to week 72, and non-inferiority of early-start versus delayed-start slopes during weeks 48 to 72 of the active phase. The UPDRS is the most commonly used rating tool to assess disease status.

Patients who received rasagiline 1-mg tablets once daily upon entry into the trial experienced a significant improvement compared with patients receiving the drug nine months later. The 1-mg dose met all three primary endpoints, as well as the secondary endpoint, with statistical significance.<sup>50</sup>

The primary analysis included three hierarchical endpoints based on total-UPDRS scores:

- superiority of slopes in weeks 12 to 36 ( $-0.05$ ;  $P = 0.013$ , 95% confidence interval [CI],  $-0.08$ ,  $-0.01$ )
- a change from baseline to week 72 ( $-1.7$  units;  $P = 0.025$ , 95% [CI],  $-3.15$ ,  $-0.21$ )
- non-inferiority of slopes (0.15 margin) in weeks 48 to 72 (0.0; 90% CI,  $-0.04$ ,  $0.04$ ).

The safety profile of rasagiline seen in ADAGIO was similar to that observed in previous experience with this agent. All three primary endpoints were met with statistical significance and reinforce the quality of the data, supporting the potential for rasagiline to slow disease progression. Delaying disease progression is the most important unmet need in the management of PD.<sup>50</sup>

Table 4 depicts the MAO-B inhibitors and their initial dosing schedule.

**Potential adverse effects and contraindications.** Several drugs are contraindicated with rasagiline because of the risk of serotonin syndrome.<sup>51</sup> Although there is little evidence to suggest the combination is actually dangerous, the potential adverse outcomes are so severe that the contraindication designation was thought to be appropriate.

Serotonergic antidepressants such as selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), and tricyclic antidepressants (TCAs) are not listed in the rasagiline product information as contraindicated, but the concomitant use of rasagiline with these agents is not recommended.<sup>51</sup> Hundreds of patients in clinical trials of rasagiline received concomitant SSRIs or TCAs, apparently without adverse interactions, but the FDA correctly noted that this does not rule out the possibility of a rare, serious adverse outcome from these combinations.<sup>51</sup> However, physicians are prescribing the concomitant

administration of selegiline and serotonergic drugs with caution, and selegiline and SSRIs have been used in combination in PD patients without adverse reactions.

**Adverse effects.** The most commonly observed adverse events affecting 5% or more patients who were receiving rasagiline as monotherapy and who were participating in the double-blind, placebo-controlled trial occurred at least 1.5 times as often as in the placebo group. These events included flu syndrome, arthralgia, depression, dyspepsia, and falls.

Treatment-emergent adverse events occurred in 2% or more of patients who received rasagiline as monotherapy and who were participating in a double-blind, placebo-controlled trial. These events occurred more frequently than in the placebo group and included headache, arthralgia, dyspepsia, depression, falling down, flu syndrome, conjunctivitis, fever, gastroenteritis, rhinitis, arthritis, ecchymosis, malaise, and neck pain.<sup>51</sup>

### Anticholinergic Agents (Muscarinic Receptor Antagonists: Artane, Cogentin, Benadryl)

Before the discovery of levodopa, antagonists of muscarinic acetylcholine receptors were widely used to treat PD, although it is not clear why such anticholinergic agents were used. They probably act within the neostriatum through the receptors that normally mediate the response to intrinsic cholinergic innervation of this structure, which arises primarily from cholinergic striatal interneurons.

Several drugs with anticholinergic properties are currently used in the treatment of PD. These are trihexyphenidyl (Artane, Wyeth), bethtropine mesylate (Cogentin, Merck) and diphenhydramine (Benadryl, Pfizer). All have modest antiparkinsonian activity that is useful in the treatment of early PD or as an adjunct to dopaminergic therapy. Anticholinergics are better tolerated in younger patients and are useful in this subgroup for tremor control.

Table 5 lists the muscarinic blocking agents and their initial dosing schedule.

**Adverse effects.** The adverse events associated with the muscarinic receptor antagonists result from their anticholinergic properties. Most problematic are sedation and mental confusion. These drugs can also produce constipation, urinary retention, and blurred vision.<sup>52</sup>

### Amantadine (Symmetrel)

Amantadine (Symmetrel, Endo) is an antiviral agent used to prevent and treat influenza A, but it also has antiparkinsonian activity. It appears to alter dopamine release in the striatum and has anticholinergic properties. Its most significant action may be its ability to block *N*-methyl *D*-aspartate (NMDA) glutamate receptors.<sup>53</sup>

Interestingly, the effects of amantadine in PD are modest. It is used as initial therapy for mild PD, and it may be helpful as an adjunct in patients taking levodopa with dose-related fluctuations and dyskinesias. The antidyskinetic properties of amantadine have been attributed to actions at NMDA receptors, although the closely related NMDA receptor antagonist memantine (Namenda, Forest) does not seem to have this effect.

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**Adverse effects.** The adverse reactions reported most frequently at the recommended dose of amantadine in 5% to 10% of patients are nausea, dizziness, lightheadedness, and insomnia.<sup>54</sup> Less frequently reported effects in 1% to 5% of patients are depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea, mild fatigue and reversible dizziness, lethargy, anticholinergic effects, livedo reticularis, and lower-extremity edema.<sup>54</sup>

### Neuroprotective Therapy (Rasagiline, Coenzyme Q10, Levodopa)

In addition to controlling the symptoms of PD, it would be advantageous to develop a therapy that modifies the progressive degeneration that governs PD. Current research strategies are based on mechanistic approaches (e.g., energy metabolism, oxidative stress, environmental triggers, and excitotoxicity) and on discoveries related to the genetics of PD.<sup>55</sup>

**The TEMPO Study.** Neuroprotective data were obtained from the Rasagiline Mesylate [TVP-1012] in *Early Monotherapy for PD Outpatients* (TEMPO) delayed-start study and are more encouraging for disease modification.<sup>56</sup> The data suggested that earlier therapy, in patients without functional impairment, results in better long-term outcomes.<sup>55</sup>

TEMPO was conducted to determine whether rasagiline monotherapy would be useful in early PD. The safety and efficacy of rasagiline, a selective MAO-B inhibitor, were determined. The study was a multicenter, 26-week, parallel-group, randomized, double-blind, placebo-controlled trial conducted in movement-disorder clinics. Patients had early PD but did not need dopaminergic therapy ( $n = 404$ ). They were randomly assigned to receive rasagiline 1 mg or 2 mg/day or a matching placebo. A one-week escalation period was followed by a 25-week maintenance period.

The main outcome measure of efficacy was the change in the total UPDRS scores between baseline and 26 weeks of treatment. Rasagiline monotherapy was effective in this 26-week study. The adjusted effect size for the total UPDRS was  $-4.20$  units comparing 1 mg of rasagiline and placebo (95% CI,  $-5.66$  to  $-2.73$  units;  $P < 0.001$ ) and  $-3.56$  units comparing 2 mg and placebo (95% CI,  $-5.04$  to  $-2.08$  units;  $P < 0.001$ ). There were no meaningful differences in the frequency of adverse events or premature withdrawals among the treatment groups. The investigators concluded that rasagiline was effective as monotherapy for patients with early PD. The two dosages in this trial were both effective in relation to placebo.<sup>56</sup>

**The Shults Study.** In one small study, coenzyme Q10 was found to slow the course in PD patients.<sup>57</sup> Coenzyme Q10 affects the energy-generating mechanisms in cells. This study suggested that treatment with 1,200 mg/day of coenzyme Q10 resulted in less disability over the fixed period of the study than lower doses of the same compound or a placebo. A larger trial is needed to confirm these findings and to determine the optimal dose of coenzyme Q10 to use.

**The Storch Study.** In this multicenter, randomized, double-blind, placebo-controlled, stratified, parallel-group, single-dose trial, nanoparticulate coenzyme Q10 at a dosage of 300 mg/day was safe and well tolerated. This dose resulted in plasma levels similar to 1,200 mg/day of standard formulations.<sup>58</sup> It was concluded that add-on coenzyme Q10 did not produce symptomatic effects in mid-stage PD.

**The ELLDOPA Study.** The *Early versus Late Levodopa* (ELLDOPA) study, conducted by the Parkinson's Study Group, was a randomized, double-blind, placebo-controlled, parallel-group, multisite clinical trial.<sup>59</sup> Participants had early PD of no more than three years' duration, but they were not otherwise receiving antiparkinson medications or symptomatic therapy.

The investigators enrolled 360 participants, dividing them randomly into four arms to receive low-dose, middle-dose, and high-dose carbidopa/levodopa, and placebo. The doses of the active-treatment groups were titrated during a course of nine weeks, to 150, 300, and 600 mg/day, respectively. After 40 weeks, a three-day washout began, followed for two more weeks without any medications. Patients were followed for 42 weeks without medication.<sup>59</sup>

The primary outcome variables were the change in severity, as measured by total UPDRS scores from baseline to week 42. The primary rater saw the participants only twice, at the baseline evaluation and at week 42, in an effort to maintain blindness. The treating investigators were also blinded, but they observed the patients throughout their course. A subset of 135 patients underwent before-and-after neuroimaging studies, for which the percentage change in the striatal dopamine transporter between baseline and week 40 assessed by cocaine analogue iodine-123-beta-CIT (beta-CIT) uptake measured by spectroscopy was the primary imaging outcome. There was no statistical difference in any baseline characteristics, including race, age, sex, or onset and duration of disease. UPDRS scores ranged from 27.3 to 29.4. Of the 361 randomized patients, 311 completed the study.<sup>59</sup>

ELLDOPA returned the most significant results in the carbidopa/levodopa 600-mg/day group, according to the primary raters. The placebo group experienced deterioration during the 40-week course and saw little change after the washout. The 150-mg/day group improved, but this effect began to be lost by 40 weeks. Greater improvement was seen in the 300- and 600-mg/day groups, and the 600-mg/day dosage maintained its effects a little longer than the 300-mg/day dosage. After two weeks of washout, patients in the 600-mg/day group were still improved over their baseline scores by 1.4 points, but the placebo group worsened by 7.8 points. These improvements were also true of

**Table 5 Muscarinic Blocking Agents for the Treatment of Parkinson's Disease**

Medication	Available Doses	Initial Dosing
Benzotropine mesylate (Cogentin)	0.5 mg 1.0 mg 2.0 mg	0.5 mg twice daily
Trihexyphenidyl HCl (Artane)	2 mg 5 mg	1–2 mg twice daily



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the motor and activities of daily living components of the UPDRS.

The treating investigators also saw these highly significant differences between the treated and placebo groups. After the washout was completed, all active-treatment groups had returned to baseline. None of the three treatment groups' UPDRS scores were ever worse than those of the placebo group, and there was no evidence of any hastening of the disease, at least after a two-week washout. The three treatments were neuroprotective because the results were better than those than in the placebo group.

Adverse events included more headaches, slightly increased muscle tone, and dystonia in patients receiving 600 mg/day. Infection, nausea, and increased somnolence were reported in the higher-dose patients, although the incidence of somnolence did not reach statistical significance. More leg pain was reported in the untreated and low-dose groups. Dopaminergic adverse events included dyskinesias and a trend for wearing-off with 600 mg/day, compared with lower doses. However, freezing was more prevalent with the lower doses than with the higher doses.

Neuroimaging results showed no differences at baseline on any of the striatal beta-CIT spectroscopy scores. At nine months, the decline in beta-CIT uptake was more pronounced in the levodopa groups than in the placebo group (−7.2%, −4%, −6%, and −1.4% with 600, 300, and 150 mg/day and placebo, respectively). This suggests contradictory results from that noted on beta-CIT spectroscopy and what was observed clinically. The evidence did not indicate that levodopa was harmful or that it hastened the progression of PD, but because of the uncertainty that levodopa's long sustained benefit might derive from a more prolonged pharmacological or plasticity effect, it cannot be concluded that levodopa proved protective.

Perhaps there might be a third type of benefit; there is a short-duration benefit and a long-duration benefit, but there might also be a more extended benefit. If so, the duration of any such benefit is unknown, and a much longer washout period than was attempted in ELLDOPA would need to be used to detect such an enduring change before neuroprotection could be confirmed.

No claims can be made from the imaging study. Interpretation is fraught with uncertainty, because the study group was small and the duration was short. It is unclear whether levodopa had an effect on dopamine binding that might explain the decreased beta-CIT uptake. Additional study is needed.

### CONCLUSION

PD generally follows a progressive course. The benefits of levodopa often diminish with time, and serious adverse effects may complicate long-term levodopa treatment. Levodopa-sparing interventions (e.g., dopamine agonist monotherapy or rasagiline in early PD), may be able to delay motor complications, whereas the initiation of levodopa might be withheld until the patient needs additional symptomatic benefit or if side effects limit the use of other agents. The symptomatic treatment of mild PD is probably best avoided until a disability or symptoms begin to affect the patient's lifestyle.

Treatment of early PD with MAO-inhibitors, dopamine agonists, or levodopa/carbidopa improves quality of life. Be-

cause there is no compelling evidence favoring any single drug, treatment should be individualized.

For the initial treatment of PD, the American Academy of Neurology recommends levodopa to improve motor disability or a dopamine agonist to lessen motor complications. After decades of clinical observation, levodopa has endured as the most effective primary medicinal agent.

Entacapone (Comtan) and rasagiline (Agilect) may be able to reduce "off" time when PD has progressed and when medications are less reliable in relieving symptoms.

Current guidelines for PD also include updates on the use of deep-brain stimulation (DBS), an emerging therapy. DBS of the subthalamic nucleus may improve motor function and reduce motor fluctuations, dyskinesia, and medication usage, although there is insufficient evidence to support DBS in other locations of the brain. More study of DBS is required.

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